REMARKS

Any fees that may be due in connection with the filing of this paper or with this application should be charged to Deposit Account No. 02-1818. If a Petition for Extension of Time is needed, this paper is to be considered such Petition. A second DECLARATION pursuant to 37 C.F.R. § 1.132 is provided.

Claims 1-23, 25, 26 and 29-45 are pending. Claims 1-23 and 30-44 are allowed. Claims 27 and 28 are cancelled without prejudice or disclaimer. Claims 25 and 26 are amended for clarity and to incorporate limitations of claim 28. Claim 29 is amended to be an independent claim and is amended for clarity. Basis for the amendment is found, *e.g.*, at paragraphs [0152] – [0153] on page 43 and paragraph [0156] on page 44. Claim 45 is amended for clarity. No new matter is added.

I. REJECTION OF CLAIMS 25-29 AND 45 UNDER 35 U.S.C. §112, 1st PARAGRAPH

Claims 25-29 and 45 are rejected under 35 U.S.C. §112, first paragraph, allegedly for containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed subject matter. The Examiner alleges that the specification provides no nexus between the modulation of the androgen receptor and a useful treatment of a disease or condition.

Claims 27 and 28 are cancelled herein without prejudice or disclaimer. Thus, as applied to claims 27 and 28, the rejection is moot. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure. 35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987).

THE CLAIMS

Claim 25 recites a method of treating an individual having a condition responsive to treatment with an androgen receptor agonist, comprising administering to the mammal a pharmaceutically effective amount of a compound of claim 1 that is an androgen receptor agonist and thereby treating the condition, where the condition is impotence, a wasting disease, hypogonadism, breast cancer, frailty, osteoporosis or cancer cachexia.

Claim 26 recites a method for treating an individual having a condition responsive to treatment with an androgen receptor antagonist, comprising administering the mammal a pharmaceutically effective amount of a compound of claim 1 that is an androgen receptor antagonist and thereby treating the condition, where the condition is acne, male-pattern baldness, hirsutism, prostatic hyperplasia or prostate cancer.

Claim 29 recites a method of providing a therapy to an individual, comprising administering to the individual a pharmaceutically effective amount of a compound of claim 1 that is an androgen receptor agonist or partial agonist, where the therapy is male hormone replacement therapy, stimulation of hematopoiesis or contraception.

Claim 45 recites a method of treating prostate cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of claim 1 that is an androgen receptor antagonist.

ANALYSIS

Summary

In maintaining the rejection, the Examiner alleges that the specification:

> does not adequately describe the nexus between the modulation of the androgen receptor and a useful treatment of a disease/condition or the specific conditions listed in claims 28, 29 or 45. Modulation of a receptor involves antagonism, inhibition, agonism and others. These modulations are sometimes opposite reactions to the same receptor. It is not seen where the instant specification adequately describes what activity the compound has that enables it to treat male pattern baldness and then [to] treat [hirsutism]. These appear to be opposite conditions to treat yet they can be treated with the same compound?

As discussed below, a) the nexus between the modulation of the androgen receptor and treatment of diseases/conditions responsive to treatment with an androgen receptor agonist, such as impotence, sexual dysfunction, a wasting disease, hypogonadism, breast cancer, osteoporosis and cancer cachexia, or an androgen receptor antagonist, such as acne, male-pattern baldness, hirsutism, prostatic hyperplasia and prostate cancer, is well known in the art; b) the specification describes the nexus between androgen receptor agonism and antagonism and specific diseases and/or condition; c) the specification provides compounds that are AR agonists or antagonists, as further evidenced by the attached DECLARATION of Dr. Lin Zhi, an inventor of the claimed subject matter, which provides data showing that the compounds have androgen receptor agonist or antagonist activity; d) the specification teaches methods for determining whether or not a compound possesses AR agonist or antagonist activity; and e) the specification provides a detailed description of methods of treating conditions/diseases mediated through androgen receptor. Therefore, because the compounds possess AR agonist or antagonist activity and compounds that have such activity are known to those skilled in the art to be used to treat diseases or conditions responsive to AR agonists or antagonists, Applicant had possession of methods of treatment of diseases or conditions responsive to AR agonists or AR antagonists.

A. The nexus between agonism of the androgen receptor (AR) and treatment of diseases/conditions responsive to AR agonists and between antagonism of the AR and treatment of diseases/conditions responsive to AR antagonists is well known

The nexus between compounds that agonize androgen receptor activity and treatment of diseases or conditions responsive to AR agonists, such as impotence, wasting diseases, hypogonadism, breast cancer, frailty, osteoporosis and cancer cachexia, and the nexus between compounds that antagonize androgen receptor activity and treatment of diseases or conditions responsive to AR antagonists, such as acne, male-pattern baldness, hirsutism, prostatic

hyperplasia and prostate cancer, was well known to those of skill in the art at the time of filing the original application. For example, Rosen *et al.* describes many diseases or conditions that were known to the skilled artisan to be mediated through modulation of the androgen receptor well before the effective filing date of the instant application (Rosen *et al.*, J. Med. Chem. 38: 4855-4874 (1995)). At page 4862, Rosen *et al.* teaches that:

> [a]ndrogens serve different functions at different stages of male development and have clear therapeutic uses in the treatment of hypogonadism, growth retardation, breast carcinoma, and osteoporosis. The actions of androgens are mediated through AR. Compounds that block the action or synthesis of androgens [anti-androgens] have proven useful in the treatment of diseases such as prostate cancer, prostatic hypertrophy, hirsutism, male pattern baldness, and acne."

Thus, years before the effective filing date of this application, those skilled in the art recognized that the actions of androgens are mediated through the androgen receptor (AR), and that compounds that block this action of androgens (AR antagonists) have proven useful in the treatment of diseases responsive to treatment with anti-androgens. Therefore, the art in this field at the effective filing date clearly provides a nexus between the treatment of such diseases as prostate cancer, prostatic hypertrophy, hirsutism, male pattern baldness and acne and antagonists of the androgen receptor.

Similarly, Rosen *et al.* recites on page 4862:

> "Androgens are synthesized in the testes, adrenal cortex, and ovaries. The net effect of endogenous androgens reflects the combined actions of the secreted hormone, testosterone; its 5α-reduced metabolite, dihydrotestosterone; and its estrogenic derivative, estradiol. Androgens serve different functions at different stages of male development and have clear therapeutic uses in the treatment of hypogonadism, growth retardation, breast carcinoma, and osteoporosis. The actions of androgens are mediated through AR."

Thus, the skilled artisan recognizes that compounds that are AR agonists have clear therapeutic uses in the treatment of hypogonadism, growth retardation, breast cancer and osteoporosis and that the action of these compounds is mediated through the androgen receptor.

Applicant respectfully submits that, at the time of the priority application, the mechanism of action of the intracellular receptors and the effects of small molecule agonists, antagonist or partial agonists on IR-mediated transcription modulation was well known to the skilled artisan (*e.g.*, see Rosen *et al.*, *supra.*). Use of androgen receptor modulators for treating various androgen receptor mediated diseases and conditions was known in the art at the effective filing date of the instant application. For example, the use and mechanism of action of testosterone and dihydrotestosterone (DHT) as androgen receptor agonists and flutamide (or its biologically active metabolite 2-hydroxyflutamide) as an androgen receptor antagonist was well known in the art (*e.g.*, see Wilson, "Androgens" in Goodman & Gilman's The

Pharmacological Basis of Therapeutics (9th ed., McGraw-Hill Health Profession Division (1996), pages 1441-1457).

1. AR agonists

Testosterone and dihydrotestosterone (DHT) are well known in the art to be androgen receptor agonists (*e.g.*, see Wilson, "Androgens" in Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th ed., McGraw-Hill Health Profession Division (1996), pages 1441-1457). Testosterone is converted to the more active DHT *in vivo*, and testosterone and DHT individually bind to the androgen receptor and act in target tissues to perform their function (*Id.*, pages 1446-1447). DHT is often is used as a standard for AR agonist activity. DHT is used to treat a number of diseases or conditions responsive to treatment with androgen receptor agonists. Alkylation of testosterone to prevent metabolic conversion has resulted in a number of stable analogs, such as fluoxymesterone. Fluoxymesterone binds to the androgen receptor and is an AR agonist *in vivo* (Kemppairen *et al.*, Mol Endrocrin 13(3): 440-454 (1999)).

Impotence

DHT has been shown to be useful for the treatment of impotence. In a randomized double-blind study, administration of transdermal DHT was found to improve sexual function and to increase the ability to maintain erection compared to the placebo group (Kunelius *et al.*, J Clin Endocrin. & Metabolism 87(4): 1467-1472 (2002)). Matsumoto reports that testosterone administration increases sexual function (Matsumoto, J Gerontology Medical Sciences 57A(2): M76-M99 (2002) at M81). Fluoxymesterone is used clinically improve sexual performance (Kemppairen *et al.*, Mol Endrocrin 13(3): 440-454 (1999)). Testosterone cypionate is indicated for treatment of impotence (*e.g.*, see Wilson, "Androgens" in Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th ed., McGraw-Hill Health Profession Division (1996), page 943).

Wasting

Testosterone and its analogs are used for the treatment of cachexia and wasting disorders (Basaria *et al.*, J Clin Endocrinol Metabol 86(11): 5108-5117 (2001)). Methyl-dihydrotestosterone is indicated for the treatment of chronic wasting diseases (*e.g.*, see *Remington's Pharmaceutical Sciences* (16th ed., Mack Publishing, Osol, ed. (1980) , page 940).

Hypogonadism

Rosen *et al.* teaches that androgens have clear therapeutic uses in the treatment of hypogonadism (J. Med. Chem. 38: 4855-4874 (1995) at page 4862). Testosterone is indicated

for the treatment of hypogonadism (*e.g.*, see *Remington's Pharmaceutical Sciences* (16th ed., Mack Publishing, Osol, ed. (1980), page 943).

Breast Cancer

DHT has been shown to inhibit mammary tumor growth by interacting with the androgen receptor, which is supported by the fact that simultaneous treatment with the anti-androgen flutamide completely prevented DHT action (Labrie, U.S. Pat. No. 5,846,960 (1998)). Clinical uses of androgens for the treatment of breast cancer have been documented (see Yin *et al.*, J Pharmacology and Experimental Therapeutics 304: 1334-1340 (2003)). Rosen *et al.* teaches that androgens have clear therapeutic uses in the treatment of breast carcinoma (J. Med. Chem. 38: 4855-4874 (1995) at page 4862). Testosterone is indicated for the treatment of breast cancer (*e.g.*, see *Remington's Pharmaceutical Sciences* (16th ed., Mack Publishing, Osol, ed. (1980), page 943).

Frailty

Frailty is a wasting syndrome of advanced age that can leave a person vulnerable to falls and often leads to functional decline. In men, frailty often accompanies andropause. DHT is considered as a treatment for andropause (de Lignieres, Annals of Medicine 25(3): 235-241 (1993)). Hamann *et al.* (J Med Chem 42: 210-212 (1999) teaches that administration of DHT has proven efficacious in abrogating age-related deterioration of muscle and bone.

Osteoporosis

Documented clinical uses of androgens include treatment of primary osteoporosis (see Yin *et al.*, J Pharmacology and Experimental Therapeutics 304: 1334-1340 (2003)). DHT also is known to influence skeletal metabolism and has been found to partially restore cancellous bone volume in osteopenic rats (Tobias *et al.*, Am J Physiol Endrocrinol Metab 267: E853-E859 (1994)). DHT stimulates bone formation (Mason *et al.*, J Bone and Mineral Research 12(9): 1431-1437 (1997) and acts directly on human osteoblastic cells via binding to the androgen receptor (Kasperk *et al.*, J Bone and Mineral Research 12(3): 464-467 (1997)). Thus, a nexus between androgen receptor agonist activity and treatment of osteoporosis is known in the art. DHT also is considered as a treatment for andropause (de Lignieres, Annals of Medicine 25(3): 235-241 (1993)), which includes as symptoms decreased bone mineral density and increased risk of osteoporosis and fractures (Matsumoto, J Gerontology Medical Sciences 57A(2): M76-M99 (2002)). Matsumoto also reports that benefits of testosterone administration include increased bone mineral density and decreased risk of osteoporosis and bone fracture (*Id.* at M81). Fluoxymesterone is used clinically to stimulate growth of the bone

matrix (Kemppairen *et al.*, Mol Endrocrin 13(3): 440-454 (1999)). Rosen *et al.* teaches that androgens have clear therapeutic uses in the treatment of osteoporosis (J. Med. Chem. 38: 4855-4874 (1995) at page 4862). Fluoxymesterone is indicated for the treatment of osteoporosis (*e.g.*, see *Remington's Pharmaceutical Sciences* (16th ed., Mack Publishing, Osol, ed. (1980), page 940).

Cancer cachexia

Hamann *et al.* (J Med Chem 42: 210-212 (1999) teaches that cancer cachexia is a clinical target of androgen therapy. Testosterone and its analogs are used for the treatment of cachexia and wasting disorders (Basaria *et al.*, J Clin Endocrinol Metabol 86(11): 5108-5117 (2001)). Methyl-dihydrotestosterone is indicated for the treatment of chronic wasting diseases (*e.g.*, see *Remington's Pharmaceutical Sciences* (16th ed., Mack Publishing, Osol, ed. (1980), page 940).

Male hormone replacement

Hamann *et al.* (J Med Chem 42: 210-212 (1999) teaches that deficiencies in circulating levels of DHT in hypogonadal men can be compensated for by administration of DHT and that administration of exogenous androgens, including DHT, have proven efficacious in hormone replacement therapy, abrogating age-related deterioration of muscle and bone, and regulating plasma lipid levels. Fluoxymesterone is indicated for male hormone replacement (*e.g.*, see *Remington's Pharmaceutical Sciences* (16th ed., Mack Publishing, Osol, ed. (1980),page 940).

Stimulation of hematopoiesis

Androgens have been used clinically for stimulating hematopoiesis and it has been shown that the androgens exert direct modulating effects on a wide spectrum of bone marrow cell types via AR-mediated responses (*e.g.*, see Mantalaris *et al.*, J Pathology 193(3): 361-366 (2001)). Fluoxymesterone is indicated for treatment of aplastic or hypoplastic anemia (*e.g.*, see *Remington's Pharmaceutical Sciences* (16th ed., Mack Publishing, Osol, ed. (1980), page 940).

Contraception

Testosterone, alone or in combination with a progesterone, has been shown to be effective in suppressing spermatogenesis, azoospermia and thus has utility as a male contraceptive (*e.g.*, see Lue *et al.*, Endocrinology 141(4): 1414-1424 (2000); Robaire *et al.*, Biology of Reproduction 31: 221-230 (1984)). Studies have shown that testosterone alone can provide almost universal azoospermia in populations with minimal side effects (Meriggiola *et al.*, J Andrology 24(4): 466-483 (2003), page 466). Multi-center trials have shown that testosterone administered in high dosages as a male hormonal contraceptive conferred an

overall contraceptive efficacy comparable to female oral contraceptives (Anawalt *et al.*, Expert Opinion on Pharmacotherapy 2(9): 1389-1398 (2001)).

Exemplary Compounds have AR agonist activity

The specification teaches that compounds within the scope of the instant claims have AR agonist activity. As demonstrated in the attached DECLARATION from Dr. Lin Zhi, a co-inventor of the claimed subject matter, 78 of the tested compounds exhibit AR agonist activity, 36 of which have AR agonist activity similar to or better than the DHT control. Thus, compounds having androgen receptor agonist activity similar to or better than DHT are effective in treating diseases or conditions for which DHT is a treatment, including impotence, wasting diseases, hypogonadism, breast cancer, frailty, osteoporosis and cancer cachexia. Compounds demonstrating AR agonist activity also are useful for hormone replacement therapy, stimulation of hematopoiesis and contraception.

2. AR antagonists

Compounds having androgen receptor antagonist activity (anti-androgens) are known to those skilled in the art to be useful in the prevention and treatment of prostate cancer, acne, seborrhea, hirsutism, androgenic alopecia and benign prostatic hyperplasia (*e.g.*, see Elbrect *et al.*, U.S. Pat. No. 5,872,150 (1999)). Among such compounds that are specific antagonists of the binding of androgens to the androgen receptor are cyproterone acetate, flutamide and spironolactone.

Cyproterone acetate is a potent anti-androgen. It acts through competitive inhibition of the androgen receptors blocking the effects of testosterone and dihydrotestosterone. Cyproterone acetate is useful in the treatment of androgen-dependent tumors, idiopathic precocious puberty, hirsutism, male pattern baldness, acne, seborrhea and benign prostatic hypertrophy (Zouboulis *et al.*, Dermatology 206(1): 37-53 (2003)).

Flutamide is a non-steroidal compound that acts only at the androgen receptor site and is devoid of other hormonal activity (Wilson, "Androgens" in Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th ed., McGraw-Hill Health Profession Division (1996), page 1453). Flutamide undergoes substantial first-pass metabolism and its biologically active metabolite is 2-hydroxyflutamide (Shulz *et al.*, Eur J Clin Pharmacol 34: 633-636 (1988)), which is a potent competitive inhibitor of DHT to the androgen receptor (Wilson, "Androgens" in Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th ed., McGraw-Hill Health Profession Division (1996), page 1453). Flutamide is useful in the treatment of acne (Zouboulis *et al.*, Dermatology 206(1): 37-53 (2003)) and hirsutism

(Moghetti *et al.*, J Clin Endocrinology & Metabolism 85(1): 89-94 (2000)). Flutamide also is used in the treatment of advanced prostate cancer (*Id.*). Spironolactone is a synthetic anti-androgen that blocks the androgen receptor (Zouboulis *et al.*, Dermatology 206(1): 37-53 (2003), page 44). Bicalutamide is an analog of flutamide and is a pure anti-androgen, demonstrating a greater affinity for the androgen receptor than 2-hydroxyflutamide. Bicalutamide functions as an androgen receptor antagonist by assembly of a transcriptionally inactive receptor and is used to treat prostate cancer (Masiello *et al.*, J Biol Chem 277(29): 26321-26326 (2002)).

Compounds having androgen receptor antagonist activity were known to be useful in the prevention and treatment of acne, hirsutism, androgenic alopecia (male pattern baldness), benign prostatic hyperplasia and prostate cancer. For example, see Singh *et al.*, Current Medicinal Chemistry 7: 211-247 (2000), which recites on page 211:

> Prostate cancer (PC), benign prostatic hyperplasia (BPH), acne, seborrhea, hirsutism and androgenic alopecia are well known to be sensitive to androgens [1,2] and to respond to androgen receptor antagonist (antiandrogen) therapy.

Rosen *et al.* (J. Med. Chem. 38: 4855-4874 (1995)) at page 4862, teaches:

> Compounds that block the action or synthesis of androgens [anti-androgens] have proven useful in the treatment of diseases such as prostate cancer, prostatic hypertrophy, hirsutism, male pattern baldness, and acne.

Acne

Cyproterone acetate is used and is effective in the treatment of acne and is considered to have proven efficacy and a long-term safety profile (see Tan *et al.*, Skin Therapy Letter 6(5), 2001, page 3; Zouboulis *et al.*, Dermatology 206(1): 37-53 (2003), page 44; Gruber *et al.*, Arch Dermatol 134: 459-463 (1998), pages 459 and 462; and Haider *et al.*, JAMA 92(6): 726-735 (2004), page 731). Flutamide also is used in the treatment of acne (see Zouboulis *et al.*, Dermatology 206(1): 37-53 (2003), page 46; and Diamanti-Kandarakis *et al.*, J Clin Endocrinol Metab 83(8): 2699 (1998), page 2704; and Haider *et al.*, JAMA 92(6): 726-735 (2004), page 731). Spironolactone also is used in the treatment of acne (Zouboulis *et al.*, Dermatology 206(1): 37-53 (2003), page 46; Shaw *et al.*, J Cutan Med Surg 6(6): 541-545 (2002), Abstract, which states that spironolactone has been used for over 20 years in the treatment of acne); Haider *et al.*, JAMA 92(6): 726-735 (2004), page 731; and Akamatsu *et al.*, J Invet Dermatol 100: 660-662 (1993), page 660.

Hirsutism

Cyproterone acetate is used to treat hirsutism (see Gruber *et al.*, Arch Dermatol 134: 459-463 (1998), pages 459; and Venturoli *et al.*, J Clin Endocrinology & Metabolism 84(4):

1304-1310 (1999), page 1307. Flutamide is used in the treatment of hirsutism (Zouboulis *et al.*, Dermatology 206(1): 37-53 (2003), page 46; Venturoli *et al.*, J Clin Endocrinology & Metabolism 84(4): 1304-1310 (1999), page 1307; Moghetti *et al.*, J Clin Endocrinology & Metabolism 85(1): 89-94 (2000), pages 89 and 93; Diamanti-Kandarakis *et al.*, J Clin Endocrinol Metab 83(8): 2699 (1998), page 2704) and Wilson, "Androgens" in Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th ed., McGraw-Hill Health Profession Division (1996), page 1454. Spironolactone also is used in the treatment of hirsutism (Moghetti *et al.*, J Clin Endocrinology & Metabolism 85(1): 89-94 (2000), pages 89 and 93; Wilson, "Androgens" in Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th ed., McGraw-Hill Health Profession Division (1996), page 1453; Bandaranayake *et al.*, CUTIS 73: 107-114 (2004), page 109; and Shaw *et al.*, J Cutan Med Surg 6(6): 541-545 (2002), Abstract, which states that spironolactone has been used for over 20 years in the treatment of hirsutism); and Akamatsu *et al.*, J Invest Dermatol 100: 660-662 (1993), page 660.

Male-pattern baldness (androgenetic alopecia)

Flutamide is used in the treatment of androgenetic alopecia (*e.g.*, see Diamanti-Kandarakis *et al.*, J Clin Endocrinol Metab 83(8): 2699 (1998), page 2704). Spironolactone also is used in the treatment of male-pattern baldness (*e.g.*, Rushton *et al.*, J Soc Cosmet Chem 42 317-325 (1991); Bandaranayake *et al.*, CUTIS 73: 107-114 (2004), page 109; and Akamatsu *et al.*, J Invet Dermatol 100: 660-662 (1993), page 660.

Benign prostatic hyperplasia

Singh *et al.* (Current Medicinal Chemistry 7: 211-247 (2000)) teaches that benign prostatic hyperplasia responds to treatment with AR antagonists. Flutamide is used in the treatment of benign prostatic hyperplasia (*e.g.*, see Liu *et* al., Bioorganic & Medicinal Chemistry 15: 4966-4972 ((2007)).

Prostate cancer

Flutamide is used in the treatment of prostate cancer (*e.g.*, see PDR, 46th edition (1992), pp. 2089-2090; and Wilson, "Androgens" in Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th ed., McGraw-Hill Health Profession Division (1996), page 1454). Cyproterone acetate also is used in the treatment of prostate cancer (*e.g.*, see Pescatore *et al.* Eur Urol. 6(3):149-153 (1980)).

Exemplary Compounds have AR antagonist activity

The specification teaches that compounds within the scope of the instant claims have AR antagonist activity. As demonstrated in the attached DECLARATION from Dr. Lin Zhi, a co-inventor of the claimed subject matter, 19 of the tested compounds exhibit AR antagonist activity. Thus, compounds with androgen receptor antagonist activity are effective in treating diseases or conditions for which an androgen receptor antagonist, such as flutamide, 2-hydroxy-flutamide or cyproterone acetate, is a treatment, such as acne, hirsutism, male pattern baldness, benign prostatic hyperplasia and prostate cancer.

B The specification teaches how to test for AR agonist or antagonist activity

The specification teaches *in vitro* assays for testing compounds, including those within the scope of the claims, for AR modulating activity, such as AR agonists or AR antagonists (*e.g.*, see pages 72-76). The assays described in the specification are known and practiced by those in the art (for example, see Berger *et al.*, J Steroid Biochem Mol Biol 41: 773-738 (1992)). Modulating activity in a co-transfection assay has been shown to correlate with *in vivo* modulating activity, and therefore such assays are predictive of *in vivo* activity (*e.g.*, see Berger *et al.*).

C. The specification provides a detailed description of methods of treating diseases/conditions mediated through androgen receptor.

The specification provides a detailed description of methods of treating diseases or conditions mediated through androgen receptor. For example, at page 43, paragraph [0152] through page 45, paragraph [0157], the specification recites:

> [0152] In certain embodiments, the invention provides methods of treating a patient comprising administering one or more compounds of the present invention. In certain embodiments, such patient suffers from a androgen receptor mediated condition. In certain embodiments, a patient is treated prophylactically to reduce or prevent the occurrence of a condition.
>
> [0153] Exemplary conditions that may be treated with one or more compounds of the present invention included, but are not limited to, acne, male-pattern baldness, wasting diseases, hirsutism, hypogonadism, osteoporosis, infertility, impotence, obesity, and cancer. In certain embodiments, one or more compounds of the present invention are used to stimulate hematopoiesis. In certain embodiments, one or more compounds of the present invention are used for contraception.
>
> [0154] In certain embodiments, one or more compounds of the present invention are used to treat cancer. Certain exemplary cancers include, but are not limited to, breast cancer, colorectal cancer, gastric carcinoma, glioma, head and neck squamous cell carcinoma, papillary renal carcinoma, leukemia, lymphoma, Li-Fraumeni syndrome, malignant pleural mesothelioma, melanoma, multiple myeloma, non-small cell lung cancer, synovial sarcoma, thyroid carcinoma, transitional cell carcinoma of urinary bladder, and prostate cancer, including, but not limited to prostatic hyperplasia.

[0155] In certain embodiments, one or more compounds of the present invention are used to improve athletic performance. In certain of such embodiments, one or more compounds of the present invention are used, for example to shorten the time normally needed to recover from physical exertion or to increase muscle strength. Athletes to whom one or more compounds of the present invention may be administered include, but are not limited to, horses, dogs, and humans. In certain embodiments, one or more compounds of the present invention are administered to an athlete engaged in a professional or recreational competition, including, but not limited to weight-lifting, body-building, track and field events, and any of various team sports.

[0156] In certain embodiments, the invention provides methods for treating a patient comprising administering one or more selective androgen receptor agonists and/or partial agonists. Exemplary conditions that may be treated with such selective androgen receptor agonists and/or partial agonist include, but are not limited to, hypogonadism, wasting diseases, cancer cachexia, frailty, infertility, and osteoporosis. In certain embodiments, a selective androgen receptor agonist or partial agonist is used for male hormone replacement therapy. In certain embodiments, one or more selective androgen receptor agonists and/or partial agonists are used to stimulate hematopoiesis. In certain embodiments, a selective androgen receptor agonist or partial agonist is used as an anabolic agent. In certain embodiments, a selective androgen receptor agonist and/or partial agonist is used to improve athletic performance.

[0157] In certain embodiments, the invention provides methods for treating a patient comprising administering one or more selective androgen receptor antagonists and/or partial agonists. Exemplary conditions that may be treated with such one or more selective androgen receptor antagonists and/or partial agonists include, but are not limited to, hirsutism, acne, male-pattern baldness, prostatic hyperplasia, and cancer, including, but not limited to, various hormone-dependent cancers, including, without limitation, prostate and breast cancer.

When read in light of the specification, the skilled artisan would understand the claimed subject matter to include methods of treatment of diseases or conditions responsive to AR agonists (or partial agonists) or AR antagonists. The specification teaches that the compounds can be used in pharmacological applications where AR antagonist or agonist activity is desired. The specification also teaches that the disclosed AR agonist, partial agonist and antagonist compounds can be useful in the treatment of conditions including hypogonadism, frailty, wasting diseases, cachexia, osteoporosis, hirsutism, acne, male-pattern baldness, prostatic hyperplasia, various hormone-dependent disorders and cancers, including prostate and breast cancer, and for male hormone replacement therapy stimulation of hematopoiesis, and as anabolic agents.

The specification teaches that the disclosed compounds can be used to treat a wide range of diseases or conditions that are responsive to treatment with an AR agonist or antagonist, describes the use of the disclosed compounds in pharmaceutical compositions, describes the preparation of pharmaceutical compositions that include the disclosed

compounds and provides working examples of such compositions (*e.g.*, see Example 56 on pages 76-78).

Conclusion

Based on the analysis, those of skill in the art could conclude that, having demonstrated AR agonist activity of exemplary disclosed compounds, and identifying conditions or diseases known in the art to be responsive to treatment with an AR agonist, including impotence, sexual dysfunction, wasting diseases, hypogonadism, osteoporosis, cancer cachexia, breast cancer, hormone replacement therapies, stimulation of hematopoiesis, male contraception and stimulation of libido, in light of what was known in the art, which teaches that the AR agonist exerts its modulating effects through the androgen receptor in these diseases or conditions, Applicant was in possession of the methods of treatment of claims 25 and 29.

Those of skill in the art also could conclude that, having demonstrated AR antagonist activity of exemplary disclosed compounds, and identifying conditions or diseases known in the art to be responsive to treatment with an AR antagonist, including acne, male pattern baldness, hirsutism, prostatic hyperplasia and prostate cancer, in light of what was known in the art, showing that the AR antagonist exerts its modulating effects through the androgen receptor in these diseases or conditions, Applicant was in possession of the methods of treatment of claims 26 and 45.

The specification provides adequate description of the claimed subject matter by describing the compounds to be used in the claimed methods, including how to make and test the compounds for the requisite activity, and identifying diseases and conditions responsive to treatment with an AR agonist or an AR antagonist. As established above, those of skill in the art recognize that compounds that exhibit activity as AR agonists/antagonists in recognized assays are used at therapeutics for diseases and conditions responsive to AR modulation. The specification teaches methods for determining whether or not a compound possesses AR agonist or antagonist activity. As demonstrated in the attached DECLARATION, exemplary compounds exhibit the requisite AR agonist or antagonist activity. Because the compounds possess AR agonist or antagonist activity, and compounds that possess AR agonist or antagonist activity are useful for the treatment of diseases/conditions responsive to treatment with AR agonists or antagonists, respectively, Applicant had possession of methods for treatment of conditions responsive to AR modulators. Therefore, the specification conveys with reasonable clarity to those skilled in the art that, as of the original filing date, Applicant was in possession of the claimed methods of treatment.

III. REJECTION OF CLAIMS 25-29 AND 45 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 25-29 and 45 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to describe the claimed subject matter in such a way as to enable one skilled in the art to make and use the claimed subject matter. The Examiner alleges that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regime on its face, that there is no showing of a nexus between any and all known diseases and the modulation of androgen receptors, that one is unable to predict possible results from administration of a compound of claim 1 due to the unpredictability of the role of modulation of androgen receptors, that *in vivo* complexity does not permit extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability, that there are no working examples of the claimed compounds working *in vivo* to treat a real-world disease or condition, that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity, and thus the result is that the specification necessitates one of ordinary skill in the art to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed methods.

Claims 27 and 28 are cancelled herein without prejudice or disclaimer. Thus, as applied to claims 27 and 28, the rejection is moot. Reconsideration of the grounds for this rejection respectfully is requested in view of the amendments herein and the following remarks.

RELEVANT LAW

The inquiry with respect to enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. The focus of the inquiry is whether everything within the scope of the claim is enabled. As concerns the breadth of a claim relevant to enablement, the only concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

It is incumbent upon the Examiner to first establish a *prima facie* case of non-enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971). The requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

> ...we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim ... What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960):

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971) (emphasis added).

The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. See *Vivid Technologies, Inc. v. American Science and Engineering, Inc.*, 200 F.3d 795, 804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999) ("patents are written by and for skilled artisans"). To hold otherwise would require every patent document to include a technical treatise for the unskilled reader. Although an accommodation to the "common experience" of lay persons may be feasible, it is an

unnecessary burden for inventors and has long been rejected as a requirement of patent disclosures. See *Atmel Corp.*, 198 F.3d at 1382, 53 USPQ2d at 1230 (Fed. Cir. 1999) ("The specification would be of enormous and unnecessary length if one had to literally reinvent and describe the wheel."); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983) ("Patents are written to enable those skilled in the art to practice the invention, not the public.")

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. The "invention" referred to in the enablement requirement of section 112 is the claimed subject matter. *Lindemann Maschinen- fabrik v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of ' 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with evidence or reasoning which is inconsistent with the contested statement.

Id. (emphasis in original); *See also Fiers v. Revel*, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993);, *Gould v. Mossinghoff*, 229 USPQ 1, 13 (D.D.C. 1985), *aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg*, 822 F.2d 1074, 3 USPQ2d 1302 ("there is no requirement in 35 U.S.C. ' 112 or anywhere else in patent law that a specification convince persons skilled in the art that the assertions in the specification are

correct"). A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987).

THE CLAIMS

The claims are discussed in a related section above.

ANALYSIS

1. Compliance with the USPTO Guidelines for "Therapeutic Compounds"

Claims 25-29 and 45 are rejected under 35 U.S.C. § 112, first paragraph, for failing to describe the claimed subject matter in such a way as to enable one skilled in the art to make and use the claimed subject matter because undue experimentation is allegedly required to demonstrate efficacy of the claimed compounds in methods of treating a real-world disease or condition.

Applicant submits that MPEP 2107.03 discusses special considerations for asserted therapeutic or pharmacological utilities, and addresses the issue of data from *in vitro* testing and its sufficiency to support therapeutic utility. MPEP 2107.03(III) states, in pertinent part, that

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. ...
>
> Evidence does not have to be in the form of data from an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates. Data from any test that the applicant reasonably correlates to the asserted utility should be evaluated substantively.

In this instance, the data presented in the attached DECLARATION of Dr. Zhi demonstrate that the claimed compounds have activity as AR agonists or antagonists. The data is from *in vitro* assays for intracellular receptors that are known and practiced by those in the art (for example, see Berger *et al.*, J Steroid Biochem Mol Biol 41: 773-738 (1992)). Those skilled in the art routinely perform these assays. Modulating activity in a co-transfection assay has been shown to correlate with *in vivo* modulating activity, and therefore such assays are predictive of *in vivo* activity (e.g., see Berger *et al.*, J Steroid Biochem Mol Biol 41: 773-738 (1992)). Because (a) the rejected claims recite methods of treating a condition responsive to administration of an AR agonist or an AR antagonist, (b) the disclosed compounds have the asserted activity, (c) assays for testing compounds for requisite activity are provided and/or known in the art, (d) the assays are routinely performed in this art, (e) the assays are predictive of *in vivo* activity and (f) diseases or conditions responsive to treatment with an AR agonist or

an AR antagonist are well known in the art, Applicant respectfully submits that it does not require undue experimentation to ascertain whether a particular compound has requisite activity and to select the compounds with the requisite activity to administer to an individual to treat a condition known to be responsive to treatment with an AR agonist or an AR antagonist. Thus, the requirements of 35 U.S.C. §112, first paragraph, have been satisfied.

2. Application of the Factors Enumerated in *In re Wands*

In addition, as discussed in detailed below, a consideration of the factors enumerated in *In re Wands* demonstrates that the application, in conjunction with what was known to one of skill in the art, teaches how to make and use the subject matter as claimed without undue experimentation.

a. The scope of the claims.

The rejected claims are directed to methods of treatment of a disease or condition that is responsive to administration of an AR agonist or AR antagonist, where the methods include administration of a compound of claim 1 that is an AR agonist or AR antagonist. For example, conditions responsive to treatment with an androgen receptor agonist include impotence, sexual dysfunction, wasting diseases, hypogonadism, osteoporosis, cancer cachexia, prostate cancer and breast cancer. AR agonist compounds also are used in other therapies, such as hormone replacement therapy, stimulation of hematopoiesis and male contraception. Conditions responsive to treatment with an androgen receptor antagonist include acne, male-pattern baldness, sexual dysfunction, hirsutism and prostatic hyperplasia.

b. Nature of the Invention

The specification provides a general description of non-steroidal compounds that are high-affinity, high-specificity agonists, partial agonists (*i.e.*, partial activators and/or tissue-specific activators) and antagonists for androgen receptors (AR). The subject matter of the rejected claims is directed to methods of treating a disease or condition responsive to administration of an AR agonist or an AR antagonist by administering a compound of claim 1 that is an AR agonist or an AR antagonist and to methods of providing therapy by administering an AR agonist.

c. State of the Prior Art

Applicant respectfully submits that, at the time of the priority application, the mechanism of action of the intracellular receptors and the effects of small molecule agonists, antagonist or partial agonists on IR-mediated transcription modulation was well known to the skilled artisan (*e.g.*, see Rosen *et al.*, J. Med. Chem. 38(25): 4855-4874 (1995)). Androgen

receptor agonist compounds and their use as therapeutic agents also were known to those skilled in the medical arts. Rosen *et al.* provides an overview of diseases and conditions that share mediation by androgen receptors as an underlying etiology. For example, Rosen *et al.* recites on page 4862:

> "Androgens are synthesized in the testes, adrenal cortex, and ovaries. The net effect of endogenous androgens reflects the combined actions of the secreted hormone, testosterone; its 5α-reduced metabolite, dihydrotestosterone; and its estrogenic derivative, estradiol. Androgens serve different functions at different stages of male development and have clear therapeutic uses in the treatment of hypogonadism, growth retardation, breast carcinoma, and osteoporosis. The actions of androgens are mediated through AR."

Applicant also submits that, at the time of the priority application, androgen receptor agonist compounds were either in clinical trials or were available to the public for the treatment of hypogonadism, metastatic breast cancer, anemias, as anabolic agents and for the treatment of other diseases or conditions. Applicant also respectfully submits that, at the time of filing the priority application, the use of androgen receptor antagonists as therapeutic agents was known to those skilled in the medical arts. For example, Singh *et al.* teaches that androgen receptor antagonists are useful for treating prostate cancer, acne, seborrhea, hirsutism and androgenic alopecia (Singh *et al.*, Current Medicinal Chemistry 7: 211-247 (2000)). Applicant also submits that, at the time of filing the instant application, several androgen receptor antagonist compounds were either in clinical trials or were available to the public for the treatment of the diseases or conditions listed above. For example, the AR antagonist cyproterone acetate was approved for the treatment of acne and hirsutism (*e.g.*, see Gruber *et al.*, Arch Dermatol 134: 459-463 (1998)).

In addition, a number of methods and assays for identifying agonists, partial agonists or antagonists of the steroid receptors were known at the time of filing the original application. For example, Berger *et al.* teaches a co-transfection assay (Berger *et al.*, J. Steroid Biochem. Molec. Biol. 41: 773-738 (1992)). Berger *et al.* teaches that activity in the co-transfection assay correlates very well with known *in vivo* activity, such that the co-transfection assay functions as a qualitative and quantitative predictor of a tested compounds *in vivo* pharmacology.

Thus, at the time of filing of the instant application, a broad body of knowledge had amassed in the areas of pharmaceutical sciences, medicine and biochemistry directed to compounds that agonize or antagonize the steroid receptors, including androgen receptors,

and to the use of compounds that agonize or antagonize androgen receptors for treatment of diseases and conditions responsive to AR agonists or antagonists.

d. Level of Skill in the Art

The level of skill in the art is high. Applicant respectfully submits that the level of skill in the medical arts is high. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, address a highly skilled audience, and further evidence the high level of skill in this art. Therefore, the amount of disclosure required to meet the enablement requirement is minimal.

e. Predictability of the Art

The Examiner states that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant application provides detailed teachings of *in vitro* assays that allow one of skill in the art to test the compounds as instantly claimed for androgen receptor modulation activity. The instant application, for example pages 72-76, provides a highly detailed teaching of *in vitro* assays, such as the "cis-trans" or "co-transfection" assay and binding assays. These assays are known in the art (see Evans *et al.*, Science 240: 889-95 (1988), are reproducible and correlate well with *in vivo* activity and can function as a qualitative and quantitative predictor of a tested compounds *in vivo* pharmacology (Berger *et al.*, J. Steroid Biochem. Molec. Biol. 41: 773-738 (1992)). As shown in the data provided in the DECLARATION of Dr. Zhi, the exemplary compounds possess androgen receptor agonist, partial agonist or antagonist activity.

As noted above, the androgen receptor agonist activity or antagonist activity shown in the *in vitro* assays correlates very well with *in vivo* activity. Once the androgen receptor activity of the compounds have been established, the application of those compounds to the treatment of any disease known to be responsive to treatment with an androgen receptor agonist or antagonist is well within the routine skills of those skilled in the art through reference to the present specification as well as the general and specialized knowledge of those working in this recognized field. Further, formulating such compounds into a pharmaceutical composition and administration of such compositions to a subject is well known in the medical arts. Thus, preparation and administration of pharmaceutical compounds also is predictable. Finally,

administration of compounds or pharmaceutical compositions is routine to one of skill in the medical arts.

f. The amount of direction or guidance presented and the presence of working examples

The Examiner alleges that the specification provides no working examples of the instantly claimed compounds working *in vivo* to treat a real-world disease or condition. The specification teaches screening assays for testing the activity of the disclosed compounds. One of skill in the art can assess the activity of any of the claimed compounds using the binding assay or the co-transfection assay, both of which are disclosed in the specification, although one of skill in the art can assess compounds using other known assays. Various screening assays for assessing the ability of a compound or composition to modulate the transcriptional ability of intracellular receptors are known to those of skill in the art, such as those described in U.S. Pat. Nos. 4,981,784, 5,071,773, 5,298,429, and 5,506,102. Further, formulating such compounds into a pharmaceutical composition and administration of such compositions to a subject is well known in the medical arts. The specification describes preparation of pharmaceutical compositions that include the disclosed compounds and provides working examples of exemplary pharmaceutical compositions (*e.g.*, see pages 76-78).

The specification teaches that compounds of formula I as claimed have AR modulating activity. For examples, see paragraph [0002] on page 1, which recites:

> This invention relates to nonsteroidal compounds that are modulators (i. e., agonists, partial agonists and antagonists) of androgen receptor, and to methods for the making and use of such compounds.

and paragraph [0093] on page 18, which recites:

> In certain embodiments, the present invention provides selective androgen receptor modulators. In certain embodiments, the invention provides selective androgen receptor binding agents. In certain embodiments, the invention provides methods of making and methods of using selective androgen receptor modulators and/or selective androgen binding agents. In certain embodiments, selective androgen modulators are agonists, partial agonists, and/or antagonists for the androgen receptor.

and paragraph [0105] on page 20, which recites:

> In certain embodiments, a compound of Formula I is a selective androgen receptor modulator. In certain embodiments, a compound of Formula I is a selective androgen receptor agonist. In certain embodiments, a compound of Formula I is a selective androgen receptor antagonist. In certain embodiments, a compound of Formula I is a selective androgen receptor partial agonist. In certain embodiments, a compound of Formula I is a tissue-specific selective androgen modulator. In certain embodiments, a compound of Formula I is a gene-specific selective androgen modulator. In certain embodiments, a compound of Formula I is a selective androgen receptor binding compound. In certain embodiments, a compound of Formula I is a selective androgen receptor modulator that also modulates one or more other nuclear receptor.

The specification also identifies compounds 101-191 as representative androgen receptor modulating compounds (see paragraph [0106] on pages 20-26). The attached DECLARATION of Dr. Zhi shows data demonstrating that what the application states is correct. As shown in the DECLARATION (see Table 3), compounds within the scope of the instant claims were tested at a concentration of 10 μM in the cotransfection assays described in Example 55 using CV-1 cells. As shown in the DECLARATION, the claimed compounds exhibit activity as androgen receptor modulators, either as agonists, partial agonists or antagonists, in the cotransfection assay described in Example 55 of the application. As demonstrated in the attached DECLARATION, 78 of the tested compounds exhibit AR agonist activity, 36 of which have AR agonist activity similar to or better than the DHT control. As demonstrated in the attached DECLARATION, 19 of the tested compounds exhibit AR antagonist activity.

g. The amount of experimentation required

There is nothing of record to suggest that use of any of the claimed compounds or compositions would require development of new procedures or excessive experimentation. As discussed above, bioassays for evaluating whether compounds are functional ligands for receptor proteins were known in the art since at least 1991 and are reproducible. Such assays are routine in this art and do not require excessive experimentation. Applicant notes that "a considerable amount of experimentation is permissible, if it is merely routine . . ." *In re Wands* 858 F.3d 731, 737 (Fed Cir. 1988). Diseases and conditions responsive to treatment with AR modulators are well known in the art. Once the AR modulating activity of the compounds have been established, the application of those compounds to the treatment of any diseases or conditions known to be responsive to androgen receptor agonists or antagonists is well within the routine skills of those skilled in the art through reference to the present specification as well as the general and specialized knowledge of those working in this recognized field.

CONCLUSION

In light of the scope of the claims, the nature of the claimed subject matter, the state of the prior art, the high level of skill of those in this art, the predictability of the art, the amount of direction and guidance presented in the specification, the presence of working examples, the low amount of experimentation required and the fact that any required experimentation is routine, Applicant respectfully submits that it would not require undue experimentation for a person skilled in the art to make and use the claimed compounds and compositions. Therefore,

the specification is enabling for making and using the full scope of the claimed subject matter. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

REBUTTAL TO THE EXAMINER'S ARGUMENTS

The Examiner states on page 2 that:

> It is not seen where the instant specification adequately describes what activity the compound has that enables it to treat male pattern baldness and then [to] treat [hirsutism]. These appear to be opposite conditions to treat yet can be treated with the same compound? Is one treated with a compound of claim 1 that is an agonist and the other treat[ed] with a compound that is an androgen inhibitor?

Applicant respectfully submits that hirsutism and male pattern baldness share an underlying etiology and are effectively treated with the same compound, *e.g.*, flutamide, cyproterone acetate, spironolactone or any other AR antagonist.

Hirsutism is the excessive growth of androgen-responsive terminal hair in women (Sakiyama, West J Med 165: 386-391 (1996)). In women with hirsutism, androgens promote an increase in the number and/or thickness of hair in unwanted areas, such as the face, neck or abdomen. Anti-androgens, *e.g.*, flutamide, cyproterone acetate and spironolactone, are used in the treatment of hirsutism because these drugs inhibit the binding of testosterone and dihydrotestosterone to the androgen receptors (*Id.* at 390).

Androgenetic alopecia occurs in men and women, and is characterized by the loss of hair from the scalp in a defined pattern (*e.g.*, see Ellis *et al.*, Expert Reviews in Molecular Medicine (19 November 2002) pages 1-11). Androgenetic alopecia occurs due to androgen dependent transformations to the hair follicles on the scalp (*Id.*). AR antagonists, *e.g.*, flutamide, cyproterone acetate and spironolactone, are used in the treatment of androgenetic alopecia (*e.g.*, see Diamanti-Kandarakis *et al.*, J Clin Endocrinol Metab 83(8): 2699 (1998), page 2704; Rushton *et al.*, J Soc Cosmet Chem 42 317-325 (1991); Bandaranayake *et al.*, CUTIS 73: 107-114 (2004), page 109; and Akamatsu *et al.*, J Invet Dermatol 100: 660-662 (1993), page 660).

Thus, although hirsutism and androgenetic alopecia may appear to be "opposite conditions" as asserted by the Examiner, they share the same underlying etiology – modification of the normal growth of hair through the action of an androgen, such as testosterone or dihydrotestosterone. Both conditions also can be treated with the same compound – an anti-androgen or AR antagonist, such as flutamide, cyproterone acetate and spironolactone.

* * *

In view of the amendments and remarks herein, reconsideration and allowance respectfully are requested.

Respectfully submitted,

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